Review of Neural Tube Defects: Risk Factors in Parental Occupation and the Environment

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We conducted a study of published work to evaluate the evidence for the hypothesis that environmental exposure and parental occupation are risk factors for neural tube defects. As other risk factors such as maternal illnesses, medication, and dietary factors have been reviewed before, this review only summarizes this information. In studies concerning environmental pollution, only a few weak associations were found. It appears that specific studies on the topic of parental occupation and neural tube defects are scarce. Therefore, studies on broader malformation categories, such as central nervous system defects, were also taken into account. Both maternal and paternal occupation seem to be associated with the occurrence of neural tube defects. However, results are not always consistent with each other, and relevant recommendations concerning prevention thus cannot be given before more studies with larger populations are conducted to confirm or refute the findings reviewed. *Key words:* chemical exposure, neural tube defects, parental occupation, risk factors. *Environ Health Perspect* 102:140–145(1994)

Neural tube defects are one of the commonest congenital malformations of the central nervous system, with an average prevalence at birth of 1 per 1000. They are caused by a failure in the process of neural tube closure. Under normal circumstances, the nervous system forms a closed tube after 4 weeks of gestation. Sometimes, for principally unknown reasons, the neural walls do not fuse. This may result in a minor or a major defect: spina bifida occulta or spina bifida aperta, respectively. When the lesion occurs in the cranial region the anomaly is called anencephaly (*1,2*).

In contrast to some other congenital malformations, neural tube defects are strongly believed to be caused by multiple factors. It was established that the frequency of spina bifida and anencephaly varies with a number of demographic factors—time, place of residence, sex, ethnic group, family history, social class, and maternal age and parity—which can be partly genetic and partly exogenous (*3*). The association of neural tube defects with socioeconomic status (higher prevalence of neural tube defects in lower socioeconomic classes) is assumed to be caused by maternal vitamin deficiency and dietary habits. Accordingly, many articles have been published about this relationship (*4*).

Another possible hypothesis for the difference in the prevalence of neural tube defects between high and low socioeconomic status is the influence of parental occupational exposure. As the classification of socioeconomic status is mainly based on the occupation of the father, occupation thus seems to be the most important component of socioeconomic status. Other exogenous factors include the occurrence of infections, alcohol consumption, smoking, and environmental pollution (*5*).

Reviews about risk factors in general and diet in particular have already been written (*3–6*). Therefore, this review does not aim to provide a complete summary but only gives a brief overview of the main risk factors for neural tube defects described in recent literature. In addition, it summarizes the available epidemiological evidence for the occupational exposure hypothesis. We consider environmental and occupational exposure extensively in order to highlight specific occupations and environmental and occupational factors that may play a part in the etiology of neural tube defects.

Materials and Methods

To evaluate all relevant articles concerning neural tube defects, spina bifida, anencephaly, and factors associated with their occurrence (especially environmental and occupational factors), we conducted an online computer search on Medline of the years 1988–1991 and on the department's literature system on reproduction and occupation with the key words "neural tube defects" or "congenital defects" in general, "environmental and occupational exposure," "industry," and "occupation." Additional papers were traced through the references listed in the articles and reviews found in the search. We selected articles concerning etiologic factors in general, whereas the articles on environmental and occupational exposure were all included. Because the results from experimental animal studies cannot easily be extrapolated to man, only human epidemiological studies were selected. Furthermore, only recent articles (the majority published after 1980) have been included in this review. Finally, the quality of the papers has not been a criterion for selection because of the small number of publications on this subject, although this factor is addressed when appropriate.

Risk Factors for Neural Tube Defects

A number of demographic factors are associated with the occurrence of neural tube defects, like time, place of residence, sex, ethnic group, family history, and social class. In relation to the social class, some exogenous factors seem to be related to the occurrence of neural tube defects (e.g., maternal illness and medication, diet, smoking, and alcohol consumption). These (possible) risk factors are discussed briefly below, followed by a more thorough consideration of occupational and environmental factors.

Sex, Race, and Place

Sex differences clearly exist in the prevalence of neural tube defects. More girls than boys are born with spina bifida (sex ratio 1/0.8); the sex ratio for anencephaly varies more widely (between 1/0.45 and 1/1) (*3*). The prevalence rates of neural tube defects also differ noticeably between geographical areas and ethnic and racial groups. Although these differences are widely accepted, Borman and Cryer (*7*) claim that geographical patterns may be attributable to variations in the design, definitions, precision, and validity of the studies used to describe these patterns. Still, it has been found that whites have higher rates than blacks; Jews have an extremely low prevalence (*8*). Data from the International Clearinghouse for Birth Defects Monitoring Systems (*9*) show that both the rates for anencephaly and spina bifida are exceptionally high in Mexico (average rates between 1985 and 1988 of 19/10,000 and 18/10,000, respectively) and in Northern Ireland (10/10,000 and 17/10,000, respectively). On the contrary, rates from Finland are as low as 1/10,000 for spina bifida, while most countries report rates between 3 and 6 per 10,000 births. As for anencephaly, the variability is somewhat greater (*9*). What is noteworthy is the suggestion by Seller (*10*) that the

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incidence of neural tube defects associated with chromosome abnormalities may be uniform and that it is the incidence of the multifactorial type (with normal chromosomes) that varies geographically. This points toward an effect of exogenous risk factors.

Time and Season

As investigated in studies of long-term trends, the prevalence of neural tube defects varies with time and season, although the trends are different among different countries. Trends in the form of an epidemic (increase of two-thirds and decrease to original level) have been observed several times. Nowadays, a worldwide decrease in prevalence figures is seen, in high as well as in low prevalence areas (*3,10–13*). One explanation for this decrease in prevalence is an increase in α-fetoprotein and ultrasound screening in pregnancy and consequent induced abortions. Adjusted prevalence figures from Stone (*12*) and from Bound et al. (*13*) (combining live births with terminations) showed, however, that antenatal screening only partly accounts for the decline in prevalence.

Seasonal fluctuations in the occurrence of neural tube defects vary with time and place. In Britain, for example, peaks were seen in spring conceptions for spina bifida and anencephaly in some areas, whereas an absence of both defects among spring conceptions was observed in South Wales. An excess of spina bifida among spring conceptions was also seen in Hungary during the 1960s (*3*). More recent data from Britain show a statistically significant peak of July conceptions, which is a constant pattern in all parts of Great Britain (*14*). No seasonal variation was proven for any malformation type in tropical or nontropical South America or in Italy (*15*).

Maternal Age, Parity, and Obstetrical History

The risk of having a child with spina bifida is found to be higher when maternal age exceeds 35; some studies also report a higher risk for mothers under 20 years of age (*3*). Feldman et al. (*16*) and Strassburg et al. (*8*), for instance, reported a statistically significant increase in the risk of neural tube defects and anencephaly with increasing maternal age. Parity has also been found to be significantly related to the risk of neural tube defects. As in age, both monotonic and U-shaped relationships (high prevalence in primiparae, low prevalence in second births and again increasing prevalence with increasing parity) have been found, the former occurring mainly in low-risk, the latter in high-risk areas. Whether maternal age or parity or both factors are responsible for the association is not entirely clear. Leck (*3*) and Roberts and Lowe (*17*) refer to a Japanese study in which the prevalence of neural tube defects in artificially interrupted pregnancies is 10 times higher than the prevalence at birth, suggesting that 90% of the neural tube defects are lost in early pregnancy and the true incidence is much higher than the reported birth prevalences. In line with this hypothesis, investigators from Finland reported that mothers with children affected by spina bifida significantly more often had a history of stillbirths [odds ratio (OR) = 4.5, $p<0.05$] and spontaneous abortions (OR = 1.8, $p<0.05$) than control mothers. The number of other live-born infants with anomalies was also higher among mothers of children with spina bifida (*18*). The previous pregnancy outcome of the mother also seems to be a risk factor for the occurrence of neural tube defects.

Siblings and Consanguinity of Parents

Relatives of people with a neural tube defect face higher risks of having a child with a neural tube defect than the general population (*18*). This risk will depend on the number of predisposing genes they have in common with the patient (*19*): 50% for first-degree relatives, 25% for second-degree relatives, and 12% for third-degree relatives. The recurrence risk of a neural tube defect is 5%. Consanguinity of parents has also been found to more than double the risk in high prevalence areas (*6*).

Socioeconomic Status

Several studies have investigated the relationship between the occurrence of neural tube defects and socioeconomic status (*20–22*). Relationships found have the same direction among different countries and for different ethnic groups: a progressive increase in the prevalence rate of neural tube defects from higher to lower socioeconomic class, as determined by the father's occupation. The biological significance of socioeconomic status is unknown. Factors such as housing conditions, frequency of infections, age at marriage, alcohol consumption, and smoking may be partly responsible for the association with neural tube defects. In addition, dietary factors such as the intake of vitamins and folic acid have been causally related to neural tube defects (*23–25*). Less has been written about the occupation of the father and mother, on which the classification of socioeconomic class is principally based. In addition to other exogenous factors, exposure to physical and chemical agents at work and environmental pollution may be logical explanations for the different prevalence rates of neural tube defects among socioeconomic classes.

Maternal Illnesses and Medication

Several years ago, associations of neural tube defects with influenza infection, the use of analgesics, and the use of antidepressants were suggested (*3*), which may indicate merely that women with a low resistance in early pregnancy are probably more liable to have affected offspring, regardless of any infection acquired or treatment received. Recently, only a few studies concerning this factor have been conducted. Saxen et al. (*26*) found no association between influenza epidemics in general and the occurrence of anencephaly, based on combined (but not linked) data on influenza epidemics in Finland and national prevalence figures of anencephaly.

After Milunsky et al. (*27*) discovered an increased incidence of neural tube defects among predominantly white insulin-dependent diabetic women (20/10,000), Zacharias and Jenkins (*28*) observed a significant increase in the incidence of neural tube defects in black insulin-dependent diabetic women, though the numbers were small. The risk in the diabetic women was 21 times that in the nondiabetic population.

Maternal epilepsy as well as the use of the anti-epileptic drug valproic acid increases the risk of spina bifida. Findings of Robert and Guibaud (*29*) of a possible relationship between valproic acid and spina bifida prompted them to conduct a case–control study. Results from this study showed an OR that was statistically significant (OR = 20.6, 95% CI: 8.2–47.9) for spina bifida and use of valproic acid during the first trimester of pregnancy, compared with other structural malformations. This high risk persisted after controlling for maternal epilepsy (OR = 17.1, 95% CI: 2.1–769) through a restriction to epileptic mothers (*30*). Lindhout and Meinardi (*31*) concluded from their data that a causal relationship existed as well. The absolute risk for spina bifida after use of valproic acid during pregnancy is believed to be 1–2%, comparable to the recurrence risk for neural tube defects (*30*). In addition, an association between the use of the anticonvulsant carbamazepine and spina bifida, controlled for valproic acid, has been described (*32*), although only small numbers were found in this cohort study. A pooled analysis of 22 cohort studies led to the conclusion that a 1% risk of spina bifida exists after carbamazepine use.

In view of the excessive use of oral contraceptives, studies have been performed to investigate the effect of their use on subsequent offspring. Kasan and Andrews (*33*) found significantly more infants with neur-

al tube defects among users of oral contraception in the 3 months before their last menstrual period or in early pregnancy compared with nonusers. In a smaller study, increased, but not statistically significant, ORs for oral contraceptive and intrauterine device use a month before pregnancy were found.

It has also been reported that women who use drugs to induce ovulation before conception are more likely to have children with neural tube defects (*5,35–37*). Whether this association is caused by the drug clomiphene or by the underlying infertility is not clear. In some studies the association has not been found at all (*38,39*).

Dietary Intake

Differences in neural tube defect prevalences, varying with time and place of residence, have been explained by different intake of vitamins, minerals, and other contents of food and drink. A high prevalence of anencephaly in the Middle East has been correlated with zinc deficiency and in England and Wales to use of water with a low mineral content (*3*). Studies considering the influence of vitamins in particular were started after it was found that the occurrence of neural tube defects was related to socioeconomic status and that vitamin levels differ between high and low socioeconomic status (*40*). The majority of research has focused on folic acid and other vitamin deficiencies. Although one (case–referent) study reported no association between periconceptional multivitamin supplementation and neural tube defects (*41*), most studies found a protective effect associated with multivitamin use or high levels of dietary folate intake (*4*). In a clinical trial by Smithells et al. (*24*), a dramatic decrease in recurrence risk after periconceptional multivitamin use was observed. The recurrence risk for supplemented women was 0.7%, compared with a recurrence risk of 4.7% for control mothers. Methodological shortcomings in both observational studies and clinical trials have been discussed extensively (*4*). Recently, a randomized, double-blind prevention trial from the Medical Research Council Vitamin Study finally provided evidence of a protective effect of folic acid: a 72% reduction of the recurrence risk of neural tube defects was found (*25*). Results from the Hungarian randomized controlled trial of multivitamin supplementation among women who had not had a prior neural tube defect-affected pregnancy were reported in 1992 (*42*). This first trial among the general population was stopped recently because of evidence of a protective effect: of 2104 women who received vitamin supplements, none had a child with a neural tube defect, compared to 6 of 2052 women who received the placebo (trace elements) supplement.

Folic acid also seems to play a role regarding other factors associated with the risk of neural tube defects, such as undergoing gastric bypass (*43*), use of oral contraceptives (*33,44*), suffering from the metabolic disorder homocysteinaemia (*45*), and the use of valproic acid and aminopterin, both of which are folic acid antagonists (*3,4*).

It has been stressed by Seller (*46*) that a deficiency of nutrients need not only result simply from a deficiency in the mother, but might also be caused by a disorder in metabolic processes. In regard to folic acid, Smithells had earlier suggested that pregnancy itself might be of more significance than changes in folate consumption (*40*). In the studies cited above, only deficiencies have been discussed as causal factors for neural tube defects. On the other hand, excessive intake of specific nutrients may also have adverse effects. An example of a teratogenic nutrient is vitamin A (*46*).

Smoking and Alcohol Consumption

Few studies have been carried out with respect to smoking and alcohol consumption as risk factors for the development of neural tube defects. Heary et al. (*47*) found a statistically significant positive association of smoking of the father with neural tube defects in a study with small sample size, which disappeared when matched analyses were performed. Recently Zhang et al. (*48*) conducted a case–referent study of paternal smoking and birth defects in a population in which paternal alcohol use and maternal smoking (both possible confounders) are rare. They found a modest relationship between paternal smoking and overall birth defects (OR = 1.2, 95% CI: 1.0–1.5); more markedly elevated risks were identified for anencephaly (OR = 2.1), spina bifida (OR = 1.9), and two other anomalies. In a Swedish study, the OR for smoking of the mother was 2.0 (95% CI: 0.9–4.6), based on information from 84 case mothers and 156 control mothers (*34*). With respect to alcohol consumption, case–studies from Castro-Gago et al. (*49*) and Friedman (*50*) report alcohol abuse in the first month of pregnancy in several mothers of infants with neural tube defects.

Environmental Pollution

It is difficult to investigate the effect of environmental pollution, and results are hard to interpret. Incidence rates have to be related to factors of pollution in a particular area, while other demographic variables have to be considered as well. Still, some studies concerning environmental pollution and neural tube defects have been conducted.

In the United States, two studies have been carried out with respect to airport noise and birth defects. In the first one, a higher-than-expected number of abnormal births, including spina bifida and anencephaly, was found in the noisiest census tracts (*51*). The authors do not automatically attribute the increased prevalence of abnormal births to jet landing noise. They suggest alternative factors such as jet aircraft pollutants, among which metallic particles are probably the most serious, and stress through the disturbance of sleep patterns (*51*). The other study (*52*) did not entirely confirm the earlier findings. No association with any category of defects was found, except for spina bifida with hydrocephalus. Because of the small number of cases, a case–referent study of all neural tube defects was done afterwards. Although the data did not rule out a slight association, no statistically significant association was found between the high-noise area and neural tube defects.

Recently, several studies have been carried out with respect to neural tube defects as a consequence of the Chernobyl accident in May 1986. In the Bursa region of Turkey, a dramatically increased frequency of neural tube defects was reported during the first 6 months of 1987 (20/1000 compared to 6/1000 between 1983 and 1986). During the period July 1987–June 1988, the total number of neural tube defects decreased gradually, supporting the hypothesis of an adverse effect of radiation (*53*). A significant increase in the incidence of neural tube defects after 1986 was also observed in the Black Sea region of Turkey (4.4/1000 compared to 2.1/1000 between 1981 and 1986, $p<0.0001$) (*54*). Although detection bias (increased detection through more attention to anomalies in that region) might have accounted for part of these increases, they might also be due to the nuclear contamination of the region after the Chernobyl accident. In Norway, no associations were found for conditions earlier reported to be associated with radiation, such as anencephaly and spina bifida (*55*).

Sever et al. (*56*) examined the prevalence of congenital malformations among two counties around the Hanford site near Richland, Washington, a nuclear power plant for the production of plutonium and electric energy. The investigators found no rates of any defects that were elevated compared with rates from the Birth Defect Monitoring Program, except for neural tube defects. A statistically significant elevated rate of 1.7 per 1000 births versus 1.0 per 1000 was observed. However, neither occupational exposure nor exposure of the general public was found to have caused the observed increase. The estimated expo-

sure represented less than a 0.05% increase over the natural background of 1 mSv, whereas the dose required to double the incidence is more than 1000 mSv. Because agriculture was an important activity in the area, the authors hypothesized that the increased rates might be related to the use of agricultural chemicals.

In this context research has been done in Australia, in which incidence rates of spina bifida and anencephaly in New South Wales and annual usage rates of the herbicide 2,4,5,-T for the whole of Australia were examined (*57*). Data covering 10 years yielded a linear correlation between a previous year's usage and the annual combined birth rate of anencephaly and spina bifida. A significant seasonal variation in birth rates of neural tube defects was also found: highest for summer conceptions, and a survey in New South Wales revealed maximum spraying during the summer months. These data cannot be taken as direct evidence of a causal association, but they are an indication that seasonal events may be important in the origin of neural tube defects. A more recent study conducted by White et al. (*58*) on birth defects in general revealed no association between pesticides used in forestry and reproductive problems. Yet, for agricultural chemicals, evidence of an association with spina bifida without hydrocephalus was found. Despite limitations in exposure assessment, the authors suggest a possible association between factors in the agricultural environment and neural tube defects.

Exposure to herbicides and pesticides may also occur through the consumption of green leafy vegetables and the use of polluted drinking water. Studies on nitrate concentrations in drinking water and the risk of neural tube defects and central nervous system defects in general have been conducted. An Australian study revealed an associaton between nitrate concentrations and the risk of neural tube defects (*59*). A more recent study (*60*) was not able to confirm these data; only weak associations were found between nitrate exposure in water and central nervous system defects. Likewise, Swedish investigators did not find associations between the occurrence of neural tube defects and average water nitrate content (*34*).

Occupational Risk Factors

So far, little has been known about the effects of parental occupational exposure on the development of neural tube defects in general or spina bifida and anencephaly in particular. Yet many studies have focused on congenital anomalies in general. Although neural tube defects often form part of that group, sample size is consequently small, and conclusions cannot be drawn with respect to neural tube defects alone. These studies are only considered here when a cluster of central nervous system defects [of which the greatest part are neural tube defects (*2*)] or a cluster of neural tube defects is sufficiently large to yield possible associations.

In a study on congenital malformations and parental occupation in Finland, women working in industrial occupations and construction had more children with central nervous system malformations than referent mothers (OR = 1.6, $p<0.05$). No statistically significant ORs were found with respect to paternal occupation. Noteworthy is the fact that differences in the risk of malformations were more pronounced for the occupational groups than for the social classes, suggesting that occupation itself or related factors determine the risk to a greater extent than social class (*61*). In a subsequent article, Hemminki et al. (*62*) report results from the same sample of cases and referents, adjusted for a number of confounding factors such as social class, tobacco smoking, and medication. Controlling for these factors increased the risk of central nervous system malformations for mothers employed in industry, construction, transport, and communication (OR = 2.0, $p<0.001$), again suggesting that social class was not responsible for the effect (*62*). A Danish study, investigating the relationship between organic solvent exposure and malformations of the central nervous system, revealed an increased risk that was statistically significant for fathers working as painters (prevalence ratio of 4.9, 95% CI: 1.4–17.1). This association was unexpected because the hypothesis concerned exposure of women. However, only two women were employed in occupations with possible exposure to organic solvents, so an association between maternal exposure and central nervous system defects could not be investigated (*63*).

Some studies indicate an increased risk for neural tube defects when congenital malformations are divided into malformation categories. Among these is the study of Holmberg and Nurminen (*64*), who found that significantly more mothers of a child with a central nervous system defect had been exposed to organic solvents during the first trimester of pregnancy compared with control mothers. Among the 14 cases of central nervous system defects in which the mother had been exposed were 8 children with anencephaly or spina bifida. Sikorski et al. (*65*) conducted a study among women in dental surgeries. Metallic mercury exposure was determined through levels in scalp and pubic hair and found to differ statistically significantly from a control group. More spontaneous abortions, stillbirths, and congenital defects occurred in dentists and dental assistants compared with the control group (24% and 11%, respectively), whereas five out of six malformations were spina bifida. A study in England on congenital malformations among offspring of agricultural workers showed that gardeners and groundsmen, who are likely to handle 2,4,5,-T, experienced increased ratios for spina bifida, anencephaly, and facial clefts [observed/expected ratios (O/E) were 123, 117, and 142, respectively], while agricultural workers had increased ratios for spina bifida and facial clefts (O/E ratio of 128 and 127, respectively) (*66*). McDonald et al. (*67*) found an association between developmental defects and fathers working in the food, beverage, and wood and textile processing industries. Among these, the observed number of neural tube defects was higher than expected (O/E ratio: 5/1.8), but sample size was small.

With respect to exposure to low-level ionizing radiation of employees of a nuclear power plant, the relation between parental occupational exposure and the risk of congenital malformations in their offspring was investigated (*68*). When all malformations were analyzed as a group, no evidence of any association was found. Analyses of fathers' cumulative exposure showed positive but nonsignificant trends; a statistically significant association was only seen for neural tube defects (mean exposure 24.2 mSv compared to an expected mean value of 13.4 mSv, $p = 0.04$), even on the basis of a small number of cases.

Recently, a registry-based case–control study of congenital defects and parental employment in health care was conducted (*70*). Offspring of mothers employed in a nursing occupation were found to be at statistically significantly increased risk of having, among others, anencephaly or spina bifida [relative risk (RR) = 2.0, 95% CI: 1.0–4.3]. The authors admit, however, that the finding of several statistically significant relative risks was expected because they estimated RRs for a large number of associations.

Only a few studies have been carried out with the specific aim of investigating the relation between neural tube defects, spina bifida, or anencephaly and parental occupational exposure. One of these studies is the Anencephalus Oxford Record Linkage Study conducted by Fedrick (*70*), in which occupations of the fathers of children with anencephaly, as described on the birth certificates, were compared with the occupations of all fathers in the area. Although numbers were small, statistically significant associations were found for

printers (RR = 6.7, $p<0.001$), painters and decorators (RR = 2.5, $p<0.005$), and transport and communication workers (RR = 1.7, $p<0.01$), who were mainly drivers of road vehicles. Maternal occupations were not considered. Hearey et al. (*47*) investigated a cluster of anencephaly and spina bifida with regard to a range of factors, including occupation and chemical exposure. The authors concluded that no exposure was associated with neural tube defects. However, this study included only 9 cases and 27 controls. A larger scale study did not reveal any significant association with maternal occupation either, although the case mothers had slightly more occupations where chemical exposure is likely (*34*). In a study investigating area differences in the prevalence of anencephaly, a slightly but significantly higher risk among mothers who reported employment during pregnancy was found (RR = 1.3, $p<0.01$) (*22*). Recently Brender and Suarez (*71*) examined the association between parental occupation and anencephalic births. Among 585 cases and 1286 controls, they especially studied whether pesticide and solvent exposure were of importance. With respect to the mothers, the number of exposed cases and controls was too low to find any exposure effect. However, women working as laborers had the highest risk for anencephalic offspring when professional, managerial, and technical women were used as a reference group. As for the fathers, exposure to solvents was associated with a significantly elevated risk for anencephalic offspring (OR = 2.5, 95% CI: 1.6–4.1). Painters had a more than threefold risk, and plastic production workers had a twofold risk. Finally, research in Venezuela (*72*) revealed remarkable differences in certain occupations between parents of children with neural tube defects and control parents. For instance, 13% of case mothers were hairdressers, compared with 1.3% of the control mothers; 8% of the case mothers were farmers and none of the controls were farmers. As for fathers, 31.6% of the cases were also farmers, compared with 13.2% among controls ($p = 0.01$) and 19.7% of fathers of cases were bricklayers, compared with 5.3% among controls ($p = 0.01$).

Discussion and Conclusion

During the past years, many studies have been conducted and much has been hypothesized concerning risk factors of neural tube defects (*5,6*). Especially the relation with dietary intake and vitamin supplementation, prompted after low socioeconomic status seemed associated with high risks, has been thoroughly examined (*4*). However, studies about environmental and occupational exposure to chemicals, also obviously related to socioeconomic status, are scarce. From the few environmental studies in this review it is clear that only a few weak associations have been found for nuclear contamination in Turkey (*53,54*), use of agricultural chemicals (*57*), and nitrate concentrations in drinking water (*59*).

The specific relation between the risk of neural tube defects and occupation of the parents has not often been investigated, and seldomly properly. In the majority of studies, registries or job titles were used instead of information about exposures given by the parents or actual measurements. Thus, because of the limited studies on neural tube defects, studies on central nervous system malformations in general were taken into account in this review. Furthermore, most of the studies involve small numbers. As case–referent studies are concerned, this means that only a few cases are found per category of occupation; as for cohort studies investigating one occupational group, this means that only a few cases occur in a specific malformation category. Also, some studies only concern occupations of the mothers, whereas others investigate only paternal occupation, the latter being biologically less plausible.

Because of the limitations and methodological differences described above, it is difficult to draw conclusions. Yet, although negative results have been found, there are some occupations that appear to have a higher risk of having offspring with neural tube defects. With regard to mothers, sample size is sometimes too small to detect any association. Still it has been found that mothers employed in industry, construction, transport, and communication have a higher risk of having offspring with central nervous system defects (*61,62*). Mothers working as dentists (*65*), hairdressers, farmers (*71*), or laborers (*70*) and mothers exposed to solvents (*64*) probably face higher risks of delivering a child with a neural tube defect. With respect to the fathers, it has been found that painters (*69,70*), printers, decorators, drivers (*69*), plastic production workers (*70*), farmers (*66,71*), those working in the food, beverage, wood and textile processing industries (*67*) and those exposed to low-level ionizing radiation (*68*) probably have a higher risk of having children with neural tube defects.

It is not very surprising that, despite differences in methodology, the different researchers have not found unequivocal results. As Little and Elwood also conclude in their review (*73*), working conditions and legislative control on occupational exposures vary between countries and within time. Because the results are not always consistent with each other, straightforward conclusions about the etiology of neural tube defects thus cannot be drawn, and relevant recommendations concerning prevention cannot be given until more specific and especially larger studies are conducted that confirm or refute the findings. Further research should not only focus on occupational title but on specific exposures and exposure levels as well. Attention should be directed toward the workers mentioned above, as these groups seem to be at an increased risk to have more infants with neural tube defects.

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